Journal of the American College of Cardiology Vol. 51, No. 1, 2008

Published by Elsevier Inc.
ISSN 0735-1097/08/$34.00
doi:10.1016/j.jacc.2007.06.063

Statins for Secondary Prevention in Elderly Patients

A Hierarchical Bayesian Meta-Analysis

Jonathan Afilalo, MD,* Gustavo Duque, MD, PHD,*† Russell Steele, PHD,‡
J. Wouter Jukema, MD, PHD,§ Anton J. M. de Craen, PHD,‖ Mark J. Eisenberg, MD, MPH*¶
Montreal, Canada; and Leiden, the Netherlands

Objectives This study was designed to determine whether statins reduce all-cause mortality in elderly patients with coronary heart disease.

Background Statins continue to be underutilized in elderly patients because evidence has not consistently shown that they reduce mortality.

Methods We searched 5 electronic databases, the Internet, and conference proceedings to identify relevant trials. In addition, we obtained unpublished data for the elderly patient subgroups from 4 trials and for the secondary prevention subgroup from the PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) trial. Inclusion criteria were randomized allocation to statin or placebo, documented coronary heart disease, ≥50 elderly patients (defined as age ≥65 years), and ≥6 months of follow-up. Data were analyzed with hierarchical Bayesian modeling.

Results We included 9 trials encompassing 19,569 patients with an age range of 65 to 82 years. Pooled rates of all-cause mortality were 15.6% with statins and 18.7% with placebo. We estimated a relative risk reduction of 22% over 5 years (relative risk [RR] 0.78; 95% credible interval [CI] 0.65 to 0.89). Furthermore, statins reduced coronary heart disease mortality by 30% (RR 0.70; 95% CI 0.53 to 0.83), nonfatal myocardial infarction by 26% (RR 0.74; 95% CI 0.60 to 0.89), need for revascularization by 30% (RR 0.70; 95% CI 0.53 to 0.83), and stroke by 25% (RR 0.75; 95% CI 0.56 to 0.94). The posterior median estimate of the number needed to treat to save 1 life was 28 (95% CI 15 to 56).

Conclusions Statins reduce all-cause mortality in elderly patients and the magnitude of this effect is substantially larger than had been previously estimated. (J Am Coll Cardiol 2008;51:37–45) © 2008 by the American College of Cardiology Foundation

Coronary heart disease (CHD) is the leading cause of death among elderly patients, with >80% of coronary deaths occurring in patients over the age of 65 (1). Despite the recommendation of the third National Cholesterol Education Program Adult Treatment Panel to intensively lower lipids in elderly patients with CHD (2–4), statin utilization continues to be 40% to 60% in elderly patients after myocardial infarction (MI) (5–8). Utilization is suboptimal because evidence has not consistently shown that statins reduce mortality in elderly patients (9–13). Thus, the primary objective of this meta-analysis was to determine whether statins reduce all-cause mortality in elderly patients with CHD and to quantify the magnitude of the treatment effect. The secondary objective was to determine whether statins reduce CHD mortality, nonfatal MI, need for revascularization, and stroke.

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From the *Department of Medicine, Sir Mortimer B. Davis Jewish General Hospital, McGill University, Montreal, Canada; †Division of Geriatrics and Bloomfield Center for Aging Research, Sir Mortimer B. Davis Jewish General Hospital, McGill University, Montreal, Canada; ‡Department of Mathematics and Statistics, McGill University, Montreal, Canada; §Division of Cardiology, Leiden University Medical Center, Leiden, the Netherlands; ‖Division of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, Netherlands; and ¶Divisions of Cardiology and Clinical Epidemiology, Sir Mortimer B. Davis Jewish General Hospital, McGill University, Montreal, Canada. Dr. Eisenberg is a Senior Physician Scientist of the Quebec Foundation for Health Research.

Manuscript received April 9, 2007; revised manuscript received May 31, 2007, accepted June 25, 2007.

Methods

We carried out this meta-analysis in accordance with standards set forth by the Quality of Reporting of Meta-Analyses of Randomised Controlled Trials (QUOROM) statement (14).

Searching. We searched Ovid MEDLINE from 1966 to December 2007 with the following search terms: hydroxymethylglutaryl-CoA reductase inhibitors, anticholesteremic agents, "fluvastatin," "pravastatin," "simvastatin," "atorvastatin," "rosuvastatin," "lovastatin," "cerivastatin,"

Abbreviations and Acronyms

CHD = coronary heart disease
CI = credible interval
MI = myocardial infarction
QUOROM = Quality of Reporting of Meta-Analyses of Randomised Controlled Trials
RCT = randomized controlled trial
RR = relative risk

randomized controlled trials (RCT), clinical trials, "randomized," myocardial infarction, and coronary disease. We searched EMBASE from 1980 to December 2007, the Cochrane Central Register of Controlled Trials and Database of Abstracts of Reviews of Effects from inception to the fourth quarter of 2007, and the ACP Journal Club from 1991 to November/December 2007. We also searched the Internet and abstracts from major cardiology conferences in North America and Europe. We used relevant references from retrieved publications and PubMed's related articles feature to identify studies not captured by our primary search strategy. Finally, we contacted investigators by telephone and e-mail to obtain unpublished data for elderly subgroups. We limited our search to human studies in any language.

Selection. The inclusion criteria for our meta-analysis were: 1) randomized allocation to statin or placebo; 2) documented CHD at the time of randomization; 3) at least 50 elderly patients included in the study (defined as age ≥65 years); 4) at least 6 months of follow-up; and 5) all-cause mortality, CHD mortality, nonfatal MI, need for revascularization, or stroke reported as an outcome measure. Three reviewers (J.A., M.J.E., G.D.) screened retrieved studies and determined whether these selection criteria were met.

Validity assessment. All qualifying studies were assessed for concealment of randomized assignment, completeness of follow-up, and intention-to-treat analysis. We recorded whether patients in the intervention and control groups were similar at the start of the study and treated equally except for the designated treatment. We also recorded whether patients in the control group were taking lipid-lowering drugs during the study. Variables reflecting internal validity and study quality are shown in Table 1.

Data abstraction. All data were extracted in duplicate by 2 investigators (J.A., M.J.E.) using a standardized protocol and reporting form and independently verified by 1 investigator (G.D.). Disagreements were resolved by consensus. We collected information on name of study, year of recruitment and publication, number of patients, duration of follow-up, inclusion and exclusion criteria, age, gender, prior MI or revascularization, coronary risk factors, medications, baseline lipid levels, change in lipid levels, intervention drug and dose, and nature of control. The outcome measures abstracted were all-cause mortality, CHD mortality, nonfatal MI, need for revascularization defined as percutaneous coronary intervention or aortocoronary bypass surgery, and stroke. We were able to extract overall study data. We did not obtain individual patient data.

Study characteristics. Differences in study and patient characteristics introduced an additional source of heterogeneity in the estimated treatment effects between trials. These differences would not be adequately dealt with in a fixed-effects meta-analysis model that uses only variability stemming from differences in sample sizes. Moreover, differences in length of follow-up would not be dealt with in a random-effects meta-analysis model. We therefore employed a Bayesian hierarchical model to account for all of these between-trial variations.

Quantitative data synthesis. In our Bayesian hierarchical model, the probability of an event within each group of each trial was allowed to vary both between the treatment and control groups within each study and between each study included in the meta-analysis. We modeled the baseline log odds of an event as normal random variables drawn from a common normal distribution, with the mean equal to the baseline log odds in the population of possible studies and variance representing the variability across studies. We similarly modeled the changes in log odds of an event attributable to treatment as normal random variables drawn from a common normal distribution, with the mean equal to the population effect of the treatment on the log odds and variance representing the variability in treatment effect across studies.

A fully Bayesian data analysis requires us to specify our prior beliefs about the population-level parameters. We used normal (mean = 0, variance = 1,000) prior distributions for all population means and regression coefficients and loosely informative inverse chi-square prior distributions for all variances to allow the data, rather than the prior distributions, to have a stronger influence on the results. Separate sensitivity analyses (not shown here) conducted with various uniform and inverse-gamma priors for the variances were found to have some effect on the estimates. Inferences were calculated with the Gibbs sampler programmed in WinBUGS software (version 1.4, MRC Biostatistics Unit, Cambridge, United Kingdom) using 3 chains and 100,000 samples per chain. Finally, we included forest plots for all major outcomes, which display the relative risks (RR) and 95% credible intervals (CI) for the individual RCTs and for the pooled results from our meta-analysis assuming a follow-up of 5 years.

Results

Trial flow. The QUOROM flow diagram is shown in Figure 1. Our search identified 729 studies, of which 66 were relevant based on their title and abstract and 16 met predetermined selection criteria. In the PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) trial, the only RCT restricted to elderly patients, primary and secondary prevention cohorts had been enrolled (10). We were able to obtain previously unpublished data for the secondary prevention cohort and incorporate them into our meta-analysis. We contacted investigators from each of the studies by telephone and e-mail to obtain unpublished data for their respective elderly patient subgroups (because 11 of

Table 1 Trial Characteristics

	Published Elderly Subgroups				Unpublished Elderly Subgroups				
	4S	CARE	LIPID	HPS	PLAC I	REGRESS	FLARE	LIPS	PROSPER
Year	1997	1998	2001	2002	1995	1995	1999	2002	2002
Mean follow-up, yrs	5.4*	5.0*	6.1	5.0	2.3	2.0	0.8	3.9*	3.2
No. of elderly	1,021	1,283	3,514	10,697	94	138	366	623	1,833
Age range, yrs	65–70	65–75	65–75	65–80	65–75	65–70	65–80	65–80	70–82
Mean age, yrs (SD)	66.8 (1.4)	69.0 (66,73)*	68.8 (2.7)	n/a	68.3 (2.6)	67.6 (1.5)	70.4 (3.7)	70.1 (3.9)	75.6 (3.4)
Inclusion criteria	MI >6 months or stable angina	MI 3–20 months	MI or unstable angina 3–36 months	Vascular disease or diabetes	Angiographic CAD or recent MI	Angiographic CAD	CAD requiring PCI	CAD requiring PCI	MI >6 months or stable angina
Study drug									
Drug	Simvastatin	Pravastatin	Pravastatin	Simvastatin	Pravastatin	Pravastatin	Fluvastatin	Fluvastatin	Pravastatin
Dose, mg/day	20-40	40	40	40	40	40	80	80	40
Nonstudy drugs									
Aspirin, %	35	82	79	63†	65	49	68	96	63
Beta-blockers, %	54	37	45	26†	18	74	57	54	33
Baseline characteristics									
Women, %	24	18	20	25†	39	0	23	22	42
Diabetes, %	5	19	10	29†	0	0	9	15	9
Smoking, %	18	12	6	14†	17	n/a	16	15	16
Hypertension, %	29	48	45	41†	57	27	38	43	46
Prior MI, %	83	100	60	41†	38	49	26	42	42
Mean baseline lipid levels, mmol/l§									
Total cholesterol	6.7	5.4	5.6	5.9†	6.0	5.8	5.5	5.1	5.7
LDL-C	4.9	3.6	3.9	3.4†	4.2	4.1	3.8	3.4	3.8
HDL-C	1.2	1.0	0.9	1.1†	1.1	0.9	1.1	1.0	1.2
Triglycerides	1.5	1.7	1.5	2.1†	1.9	1.6	1.5	1.6	1.6
Mean change in lipid levels, %									
Total cholesterol	−26	−20	−19	−20†	−19	−19	−23	−17	n/a
LDL-C	−36	−29	−28	−29†	−28	−27	−32	−24	−32‡
HDL-C	+7	+4	+7	+3†	+8	+9	+4	−1	+5‡
Triglycerides	−14	−12	−11	−14†	−10	−13	−5	−2	−12‡
Study quality									
Follow-up, %	100	>99	>99	>99	78	>99	95	99	89‡
Intention-to-treat	Yes	Yes	Yes	Yes	Yes	n/a	Yes	Yes	Yes
Double-blind	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

*Median (Q1, Q3). †Data from the published cohort of young and elderly patients. ‡Data from the published cohort of primary and secondary prevention patients. §To convert total cholesterol, LDL-C, and HDL-C from mmol/l to mg/dl, divide by 0.02586. To convert triglycerides from mmol/l to mg/dl, divide by 0.01129.

CAD = coronary artery disease; MI = myocardial infarction; LDL-C = low-density-lipoprotein cholesterol; HDL-C = high-density-lipoprotein cholesterol; n/a = not available; MI = myocardial infarction; PCI = percutaneous coronary intervention.

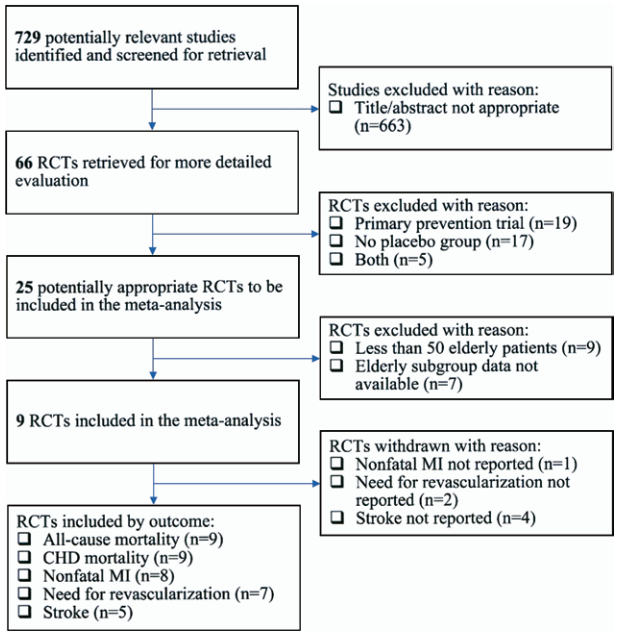

Figure 1 **QUOROM Flow Diagram**

CHD = coronary heart disease; MI = myocardial infarction; QUOROM = Quality of Reporting of Meta-Analyses; RCT = randomized controlled trial.

the 16 RCTs did not explicitly report results for this subgroup). In total, we obtained elderly patient data from 9 RCTs: 4 from published sources (15–18) and 5 from unpublished sources (10,19–22). Unpublished data were extracted from the original RCT databases and provided in writing by the investigators of the RCTs. The elderly patient subgroup analysis from the CARE (Cholesterol And Recurrent Events) trial had been previously published but did not report the all-cause mortality data. We were able to obtain these data from the investigators, and they are presented in Figure 2.

Study characteristics. The trial characteristics are shown in Table 1. There were 9 RCTs: REGRESS (REgression GRowth Evaluation Statin Study) (22), PLAC I (Pravastatin Limitation of Atherosclerosis in the Coronary arteries I) (19), 4S (Scandanavian Simvastatin Survival Study) (15,23), CARE (16,24), FLARE (FLuvastatin Angiographic REstenosis) (20), LIPID (Long-term Intervention with Pravastatin in Ischaemic Disease) (17,25), LIPS (Lescol Intervention Prevention Study) (21), PROSPER (10), and HPS (Heart Protection Study) (18,26). These RCTs were published between 1995 and 2002. The total number of elderly patients was 19,569, and the mean weighted follow-up period was 4.9 years (95,929 patient-years). In HPS, 35% of patients were enrolled on the basis of noncoronary vascular disease and 1% on the basis of high-risk hypertension. We conducted analyses with and without this trial. Among control-group patients, the utilization of lipid-lowering drugs varied between 2% and 24%, although analyses were conducted on an intention-to-treat basis in 8 out of 9 RCTs. The primary outcome measure was major adverse cardiac events in 6 of 9 RCTs and angiographic progression of coronary artery disease in FLARE, PLAC I, and REGRESS.

Quantitative data synthesis. Figures 2 to 6 show Bayesian forest plots with the posterior relative risk estimates for each study and the pooled relative risk estimates for 5 years of follow-up. The value of follow-up used for the pooled estimates did not noticeably affect the results. We estimated a relative risk reduction of 22% for all-cause mortality (RR 0.78; 95% CI 0.65 to 0.89). The posterior median estimate of the number needed to treat to save 1 life was 28 (95% CI 15 to 56). Coronary heart disease mortality was reduced

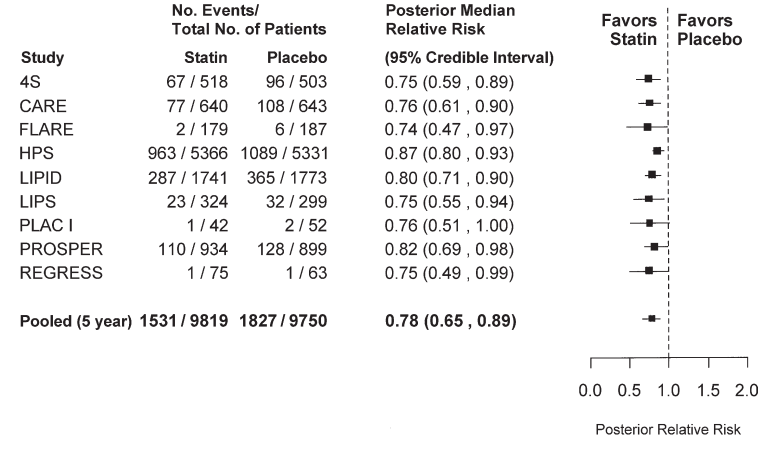

Figure 2 **Bayesian Forest Plot for All-Cause Mortality**

Statin therapy reduced the incidence of all-cause mortality by 22% over 5 years as compared to placebo. The posterior median estimate of the number need to treat was 28.

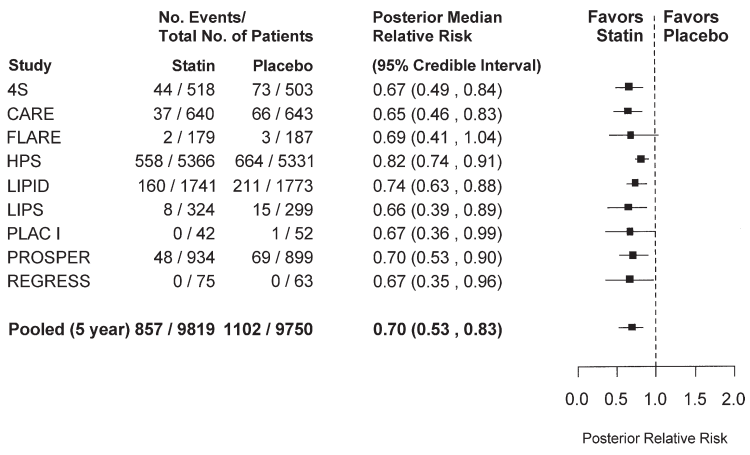

Figure 3 **Bayesian Forest Plot for Coronary Heart Disease Mortality**

Statin therapy reduced the incidence of coronary heart disease mortality by 30% over 5 years as compared to placebo. The posterior median estimate of the number need to treat was 34.

by 30% (RR 0.70; 95% CI 0.53 to 0.83), with a number needed to treat of 34 (95% CI 18 to 69). Nonfatal MI was reduced by 26% (RR 0.74; 95% CI 0.60 to 0.89), with a number needed to treat of 38 (95% CI 16 to 118). Need for revascularization was reduced by 30% (RR 0.70; 95% CI 0.53 to 0.83), with a number needed to treat of 24 (95% CI 12 to 59). Stroke was reduced by 25% (RR 0.75; 95% CI 0.56 to 0.94), with a number needed to treat of 58 (95% CI 27 to 177).

Sensitivity analysis. Standard convergence diagnostics such as those proposed by Gelman and Rubin (27,28) and Raftery and Lewis (29) showed that all 3 chains for the 4 outcomes converged quite quickly. We conducted a substantial sensitivity analysis to evaluate our choice of prior distributions. Typically, Bayesian hierarchical model inferences are most sensitive to the choice of prior distributions for the variances of the baseline and treatment random effects. Owing to the small number of studies used in our analysis, we found that our results were sensitive to different choices of prior distribution for the variances. However, to obtain pooled relative risk intervals that contained 1.0 for any particular outcome, one would have to use prior distributions that would imply strong a priori beliefs that variability between studies would be large.

We also experimented with a uniform prior over a wide interval and obtained similar results to those obtained with the inverse chi-square priors. It should also be noted that the magnitude of the treatment effect does increase as one increases a prior variability; it is the precision of the interval that affects interpretation of the results. The proportion of

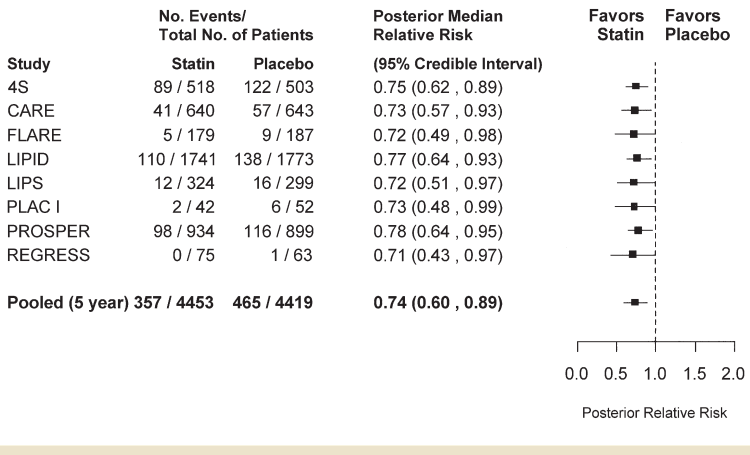

Figure 4 **Bayesian Forest Plot for Nonfatal Myocardial Infarction**

Statin therapy reduced the incidence of nonfatal myocardial infarction by 26% over 5 years as compared to placebo. The posterior median estimate of the number need to treat was 38.

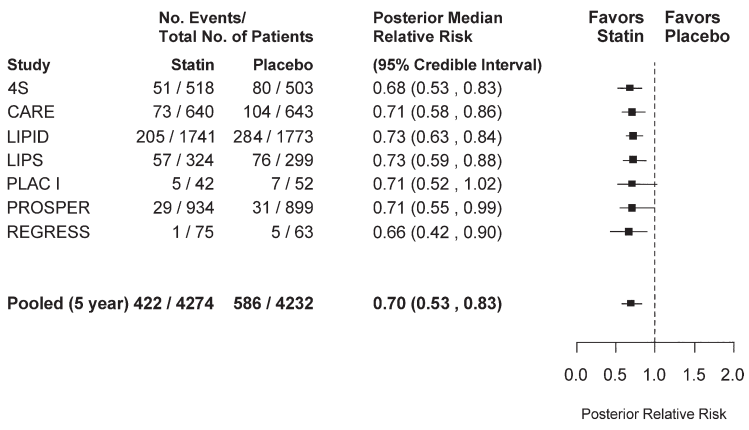

Figure 5 **Bayesian Forest Plot for Revascularization**

Statin therapy reduced the need for revascularization (percutaneous coronary intervention or aortocoronary bypass surgery) by 30% over 5 years as compared to placebo. The posterior median estimate of the number need to treat was 24.

patients with prior MI had been identified as a potential confounder because of significant variability between trials (26% to 100%) and questionable treatment effects in low-risk populations. We conducted Bayesian analyses adjusting for the proportion of patients with prior MI (including analyses with and without the HPS trial) and found that the treatment effects remained consistent. Finally, we conducted unadjusted non-Bayesian Frequentist analyses and again found that the treatment effects remained consistent.

Discussion

In elderly patients with documented CHD, statins reduce all-cause mortality by 22%, CHD mortality by 30%, non-fatal MI by 26%, need for revascularization by 30%, and stroke by 25%. These estimates are rigorous and precise, owing in large part to our Bayesian hierarchical model and larger sample size of elderly patients, who had historically been under-represented in clinical trials. Achieving a high level of precision was critical, because summary odds ratios for all-cause mortality from 23 meta-analyses had been variable and heterogeneous (9). Contemporary meta-analyses suggested that the relative reduction in all-cause mortality was similar in young and elderly patients, with a modest number needed to treat of 56 to 61 and an upper confidence interval limit approaching 100 (30,31). Our meta-analysis shows that the absolute benefit of statin therapy was underestimated in the elderly patient population, with a number needed to treat for all-cause mortality of 28 and a narrower credible interval.

Our meta-analysis supports the value of statins in RCT patients starting therapy at 65 to 82 years of age. Extrapolation to older "real-world" patients is supported by obser-

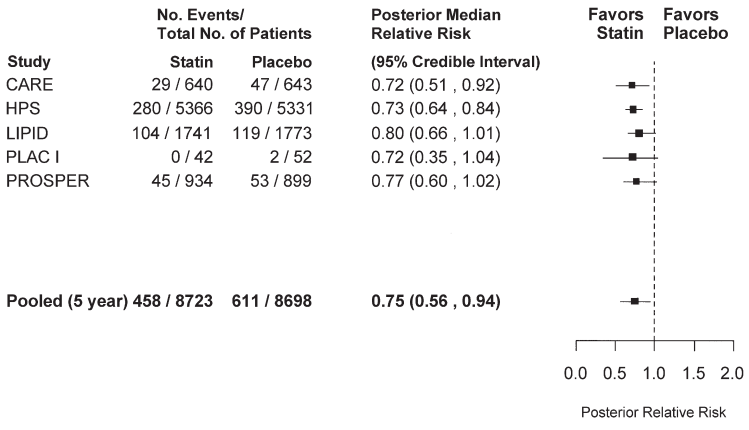

Figure 6 **Bayesian Forest Plot for Stroke**

Statin therapy reduced the incidence of stroke by 25% over 5 years as compared to placebo. The posterior median estimate of the number need to treat was 58.

vational studies (32,33) and by statistical analysis of baseline risk and number needed to treat (34). The largest observational study showed that statins reduced all-cause mortality in patients with angiographically proven coronary artery disease up to 97 years of age (32). One of the most interesting findings of this study was that older patients attained a greater reduction than younger patients; the relative risk reduction for all-cause mortality was 50% in patients aged 80 to 97, 44% in patients aged 65 to 79, and 30% in patients aged <65 years. Assuming a relative risk reduction that is greater than or equal to younger patients, the absolute risk reduction will be greater in the elderly because it is a function of baseline risk. Elderly patients have a higher baseline risk of mortality; therefore, they have a greater absolute risk reduction and a lower number needed to treat (34).

Skepticism regarding the effects of statin therapy in elderly patients surfaced after the PROSPER trial (11). The PROSPER trial recruited patients 70 to 82 years of age with cardiovascular risk factors (primary prevention cohort) or documented cardiovascular diseases (secondary prevention cohort). The results of this trial did not suggest any discernible effect of statin therapy on all-cause mortality. The published PROSPER trial did not report all-cause mortality results stratified by primary and secondary prevention cohorts; however, the unpublished PROSPER data obtained for this meta-analysis showed that the secondary prevention cohort did derive a significant benefit in all-cause mortality (Fig. 2). As may have been expected (35), the primary prevention cohort did not derive a significant benefit and diluted the overall effect estimate.

In addition to the modest results of the PROSPER trial and the heterogeneous odds ratios reported by meta-analyses, safety and cost concerns limit the use of statins in elderly patients. Available evidence suggests that these concerns may be exaggerated. We did not pool adverse events and cost effectiveness because of failure to report these events stratified by age group in most studies and inconsistencies in classification of these events between studies.

The LIPID study and the Cholesterol Reduction in Seniors Program showed that the incidence of hepatic, muscular, dermatologic, respiratory, genitourinary, gastrointestinal, and traumatic adverse events were similar in patients <65 and >65 years of age (17,36). HPS and the Cholesterol Treatment Trialists showed that the incidence of nonvascular death from cancer or other causes was similar in patients treated with statins or placebo (18,37). Two meta-analyses focused on the effect of statins on cancer risk concluded that statins have a neutral effect on overall and site-specific cancer incidence and death (38,39). 4S and the Pravastatin Pooling Project showed that the rate of treatment discontinuations because of any adverse event was surprisingly increased in patients treated with placebo (15,40). The reason for this is unclear, but the authors hypothesized that placebo-treated patients suffered adverse events as a result of not taking statins. Furthermore, the PROSPER trial showed that the effect of polypharmacy, where patients were taking up to 16 concomitant drugs, did not negate the benefits of statins (41). One explanation may be because pravastatin is not metabolized by cytochrome P450 and thus has low potential for drug–drug interactions. An overview of statin safety and drug interactions (42), as well as meta-analyses of statin-related adverse events, have been previously published (43,44).

The cost-effectiveness ratio of statins was shown to be $18,800 per quality-adjusted life-year in patients aged 75 to 84 years (45–47) (comparable to the cost of commonly accepted treatments such as treating hypertension in adults ages 35 to 64 years). Like the number needed to treat, the cost-effectiveness ratio is a function of baseline risk. Therefore, the cost-effectiveness ratio is favorable in the elderly patient population because they have a higher risk of mortality and morbidity.

Women represented one-quarter of patients in our elderly subgroups, which is greater than the proportion in the nonelderly subgroups but less than the true proportion in the aging population. Although women continue to be under-represented in clinical trials, it is reassuring to note that gender was not a significant effect modifier in these RCTs. The magnitude of the relative risk reduction for mortality or major morbidity was similar in men and women (confidence intervals sometimes crossed unity in women as a result of insufficient sample size and power).

Our study has several potential limitations. First, subgroup analyses must be interpreted cautiously because of failure to account for multiple hypotheses and, as a result, a risk of finding spurious subgroup effects (48). We believe that this risk is minimal in our meta-analysis because we analyzed similar subgroups across independent RCTs and did not observe qualitative differences. The majority of the RCTs stratified randomization by age group, further reducing the risk of unbalanced randomization. Second, we did not identify any placebo-controlled RCTs of secondary prevention for newer statins such as atorvastatin and rosuvastatin. This issue is mitigated by a study that showed that different statins were equally effective (class effect) for secondary prevention of CHD in elderly patients (49). Lastly, we were unable to obtain elderly-patient data from 7 RCTs. It is unlikely that these RCTs would change our results, because their respective patient characteristics and overall results were similar to the included RCTs and their sample sizes were relatively small. Moreover, we were able to obtain unpublished data from several sources. Published trials tend to favor the intervention, and meta-analyses restricted to published trials tend to overrepresent the actual effect (publication bias). To our knowledge, no other meta-analysis has reported unpublished data for the elderly patient population.

Conclusions

The use of statins for secondary prevention of cardiovascular events is commonly accepted in young and elderly patients. Our meta-analysis adds to the current body of literature by showing that statins reduce all-cause mortality in elderly patients and that the magnitude of this effect is substantially larger than previously estimated. In addition, statins reduce nonfatal major adverse cardiac events, which have been shown to increase the risk of functional decline and permanent disability in older adults (50,51), especially those who are frail (52,53). Despite the fact that older patients derive the most benefit at the lowest cost, old age is still an independent risk factor for underutilization of statins (54). There has been a global increase in statin utilization with the emergence of RCT evidence in the past 5 years (55–57) and a few regional increases with the use of knowledge translation programs and quality control initiatives (58–60). However, recently reported utilization rates of 40% to 60% in elderly patients with active CHD remain suboptimal (5–8). It is crucial to disseminate the evidence for statins in elderly patients with CHD to increase current utilization rates.

Acknowledgments

The authors thank Dr. Sandra J. Lewis (CARE), Dr. Andrew Tonkin (LIPID), Dr. Rene Belder (PLAC I, REGRESS), and Dr. Michele Bortolini (FLARE, LIPS) for providing unpublished elderly patient data from their respective trials.

Reprint requests and correspondence: Dr. Mark J. Eisenberg, 3755 Cote Ste Catherine, Suite A-118, Montreal, Quebec H3T 1E2, Canada. E-mail: mark.eisenberg@mcgill.ca.

REFERENCES

1. American Heart Association. Older Americans and cardiovascular diseases—statistics. Available at: http://www.americanheart.org/downloadable/heart/1168618073572OLDER07.REV.pdf. Accessed December 3, 2007.
2. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
3. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143–421.
4. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. J Am Coll Cardiol 2004;44:720–32.
5. Foody JM, Roe MT, Chen AY, et al. Lipid management in patients with unstable angina pectoris and non-ST-segment elevation acute myocardial infarction (from CRUSADE). Am J Cardiol 2005;95:483–5.
6. Harder S, Fischer P, Krause-Schafer M, et al. Structure and markers of appropriateness, quality and performance of drug treatment over a 1-year period after hospital discharge in a cohort of elderly patients with cardiovascular diseases from Germany. Eur J Clin Pharmacol 2005;60:797–805.
7. Philippe F, Danchin N, Quentzel S, Cambou JP. Utilization of the principle therapeutic classes for cardiovascular prevention in elderly patients seen by cardiologists. The ELIAGE survey (in French). Ann Cardiol Angeiol (Paris) 2004;53:339–46.
8. Pilote L, Beck CA, Karp I, et al. Secondary prevention after acute myocardial infarction in four Canadian provinces, 1997–2000. Can J Cardiol 2004;20:61–7.
9. Katerndahl DA, Lawler WR. Variability in meta-analytic results concerning the value of cholesterol reduction in coronary heart disease: a meta-meta-analysis. Am J Epidemiol 1999;149:429–41.
10. Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360:1623–30.
11. Little PJ. The PROSPER trial. Lancet 2003;361:428.
12. Lewis SJ. Statin therapy in the elderly: observational and randomized controlled trials support event reduction. Am J Geriatr Cardiol 2004;13:10–6.
13. Raffel OC, White HD. Drug insight: statin use in the elderly. Nat Clin Pract Cardiovasc Med 2006;3:318–28.
14. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999;354:1896–900.
15. Miettinen TA, Pyorala K, Olsson AG, et al. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: findings from the Scandinavian Simvastatin Survival Study (4S). Circulation 1997;96:4211–8.
16. Lewis SJ, Moye LA, Sacks FM, et al. Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. Results of the Cholesterol and Recurrent Events (CARE) trial. Ann Intern Med 1998;129:681–9.
17. Hunt D, Young P, Simes J, et al. Benefits of pravastatin on cardiovascular events and mortality in older patients with coronary heart disease are equal to or exceed those seen in younger patients: results from the LIPID trial. Ann Intern Med 2001;134:931–40.
18. Heart Protection Study Collaborative Group. The effects of cholesterol lowering with simvastatin on cause-specific mortality and on cancer incidence in 20,536 high-risk people: a randomised placebo-controlled trial. BMC Med 2005;3:1–31.
19. Pitt B, Mancini GB, Ellis SG, Rosman HS, Park JS, McGovern ME. Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): reduction in atherosclerosis progression and clinical events. PLAC I investigation. J Am Coll Cardiol 1995;26:1133–9.
20. Serruys PW, Foley DP, Jackson G, et al. A randomized placebo-controlled trial of fluvastatin for prevention of restenosis after successful coronary balloon angioplasty; final results of the fluvastatin angiographic restenosis (FLARE) trial. Eur Heart J 1999;20:58–69.
21. Serruys PW, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. JAMA 2002;287:3215–22.
22. Jukema JW, Bruschke AV, van Boven AJ, et al. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS). Circulation 1995;91:2528–40.
23. Scandinavian Simvastatin Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9.
24. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996;335:1001–9.
25. The Long-Term Intervention with Pravastatin in Ischaemic Disease Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. N Engl J Med 1998;339:1349–57.
26. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7–22.
27. Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. Stat Sci 1992;7:457–511.

28. Gelman A, Carlin JB, Stern HS, Rubin DB. Bayesian Data Analysis. 2nd edition. Boca Raton, FL: CRC Press, 2003.
29. Raftery AE, Lewis SM. How many iterations in the Gibbs sampler? In: Bernardo JM, Berger JO, Dawid AP, Smith AFM, editors. Bayesian Statistics 4. Oxford: Oxford University Press, 1992:763–73.
30. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. JAMA 1999; 282:2340–6.
31. Wilt TJ, Bloomfield HE, MacDonald R, et al. Effectiveness of statin therapy in adults with coronary heart disease. Arch Intern Med 2004;164:1427–36.
32. Allen Maycock CA, Muhlestein JB, Horne BD, et al. Statin therapy is associated with reduced mortality across all age groups of individuals with significant coronary disease, including very elderly patients. J Am Coll Cardiol 2002;40:1777–85.
33. Aronow WS, Ahn C. Incidence of new coronary events in older persons with prior myocardial infarction and serum low-density lipoprotein cholesterol ≥125 mg/dl treated with statins versus no lipid-lowering drug. Am J Cardiol 2002;89:67–9.
34. Alter DA, Manuel DG, Gunraj N, Anderson G, Naylor CD, Laupacis A. Age, risk-benefit trade-offs, and the projected effects of evidence-based therapies. Am J Med 2004;116:540–5.
35. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs. usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002;288:2998–3007.
36. LaRosa JC, Applegate W, Crouse JR III, et al. Cholesterol lowering in the elderly. Results of the Cholesterol Reduction in Seniors Program (CRISP) pilot study. Arch Intern Med 1994;154:529–39.
37. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005; 366:1267–78.
38. Dale KM, Coleman CI, Henyan NN, Kluger J, White CM. Statins and cancer risk: a meta-analysis. JAMA 2006;295:74–80.
39. Bonovas S, Filioussi K, Tsavaris N, Sitaras NM. Statins and cancer risk: a literature-based meta-analysis and meta-regression analysis of 35 randomized controlled trials. J Clin Oncol 2006;24:4808–17.
40. Pfeffer MA, Keech A, Sacks FM, et al. Safety and tolerability of pravastatin in long-term clinical trials: prospective Pravastatin Pooling (PPP) Project. Circulation 2002;105:2341–6.
41. Shepherd J. Preventing the next event in the elderly: the PROSPER perspective. Atheroscler Suppl 2003;4:17–22.
42. Bottorff MB. Statin safety: what to know. Am J Geriatr Cardiol 2004;13:34–8.
43. Silva MA, Swanson AC, Gandhi PJ, Tataronis GR. Statin-related adverse events: a meta-analysis. Clin Ther 2006;28:26–35.
44. Kashani A, Phillips CO, Foody JM, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. Circulation 2006;114:2788–97.
45. Ganz DA, Kuntz KM, Jacobson GA, Avorn J. Cost-effectiveness of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor therapy in older patients with myocardial infarction. Ann Intern Med 2000; 132:780–7.
46. Goldman L, Weinstein MC, Goldman PA, Williams LW. Cost-effectiveness of HMG-CoA reductase inhibition for primary and secondary prevention of coronary heart disease. JAMA 1991;265: 1145–51.
47. Mihaylova B, Briggs A, Armitage J, Parish S, Gray A, Collins R. Cost-effectiveness of simvastatin in people at different levels of vascular disease risk: economic analysis of a randomised trial in 20,536 individuals. Lancet 2005;365:1779–85.
48. Yusuf S, Wittes J, Probstfield J, Tyroler HA. Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. JAMA 1991;266:93–8.
49. Zhou Z, Rahme E, Abrahamowicz M, et al. Effectiveness of statins for secondary prevention in elderly patients after acute myocardial infarction: an evaluation of class effect. Can Med Assoc J 2005; 172:1187–94.
50. van Jaarsveld CH, Sanderman R, Miedema I, Ranchor AV, Kempen GI. Changes in health-related quality of life in older patients with acute myocardial infarction or congestive heart failure: a prospective study. J Am Geriatr Soc 2001;49:1052–8.
51. Mendes de Leon CF, Bang W, Bienias JL, Glass TA, Vaccarino V, Kasl SV. Changes in disability before and after myocardial infarction in older adults. Arch Intern Med 2005;165:763–8.
52. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56: M146–56.
53. Alexander KP, Newby LK, Cannon CP, et al. Acute coronary care in the elderly, part I: non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. Circulation 2007;115:2549–69.
54. Fonarow GC, French WJ, Parsons LS, Sun H, Malmgren JA. Use of lipid-lowering medications at discharge in patients with acute myocardial infarction: data from the National Registry of Myocardial Infarction 3. Circulation 2001;103:38–44.
55. Yarzebski J, Spencer F, Goldberg RJ, Lessard D, Gore JM. Temporal trends (1986–1997) in cholesterol level assessment and management practices in patients with acute myocardial infarction: a population-based perspective. Arch Intern Med 2001;161:1521–8.
56. Ayanian JZ, Landrum MB, McNeil BJ. Use of cholesterol-lowering therapy by elderly adults after myocardial infarction. Arch Intern Med 2002;162:1013–9.
57. Teeling M, Bennett K, Feely J. The influence of guidelines on the use of statins: analysis of prescribing trends 1998–2002. Br J Clin Pharmacol 2005;59:227–32.
58. Ghosh S, Aronow WS. Utilization of lipid-lowering drugs in elderly persons with increased serum low-density lipoprotein cholesterol associated with coronary artery disease, symptomatic peripheral arterial disease, prior stroke, or diabetes mellitus before and after an educational program on dyslipidemia treatment. J Gerontol A Biol Sci Med Sci 2003;58:M432–5.
59. Strandberg TE, Pitkala K, Berglind S, Nieminen MS, Tilvis RS. Possibilities of multifactorial cardiovascular disease prevention in patients aged 75 and older: a randomized controlled trial: Drugs and Evidence Based Medicine in the Elderly (DEBATE) study. Eur Heart J 2003;24:1216–22.
60. LaBresh KA, Ellrodt AG, Gliklich R, Liljestrand J, Peto R. Get with the guidelines for cardiovascular secondary prevention: pilot results. Arch Intern Med 2004;164:203–9.